EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201300107

# (β-D-Ribofuranosyl)formamidine in the Design and Synthesis of 2-(β-D-Ribofuranosyl)pyrimidines, Including $R^F$-Containing Derivatives

**Viktor O. Iaroshenko,*[a,b] Sergii Dudkin,[a] Vyacheslav Ya. Sosnovskikh,[c] Alexander Villinger,[a] and Peter Langer*[a,d]**

**Keywords:** Nucleosides / Drug design / Drug discovery / Fluorine / Ribonucleosides / Alkynes

A wide range of novel 2-(β-D-ribofuranosyl)pyrimidines, including $R^F$-containing derivatives, have been synthesized by the reaction of (β-D-ribofuranosyl)formamidine with various dielectrophilic substrates such as 3-alkoxy- and 3-chloro-1-(polyfluoroalkyl)propen-1-ones, 3-nitro- and 3-(phenylethynyl)chromones and heteroaryl acetylenic ketones.

## Introduction

Substituting hydrogen by fluorine in organic compounds is one of the most powerful synthetic tools available to influence a variety of molecular properties. The strategy has been widely applied in medicinal chemistry and drug design as a way of tuning metabolic stability, modifying chemical reactivity, and improving transportation and absorption characteristics of pharmaceuticals.[1] The presence of fluorine in drug candidates and marketed drugs is now commonplace. The impact made by fluorine on molecular properties has been well-studied and described in the literature.[1,2] To date there are more than 200 pharmaceuticals known with at least one fluorine atom. Literature analysis highlights the presence of fluorine in 10–15% of launched drugs worldwide over the past 50 years, with a noticeable increase in the past five years.[1b] One can find fluorine in pharmaceuticals and drug candidates in a variety of structural presentations, for instance, molecules containing between 1 and 21 fluorine atoms are applicable in all therapeutic areas.

Pivotal positions among all classes of fluorinated pharmacologically active compounds have been occupied by nucleosides with fluorine functionality either in the sugar or in the heterocyclic part. Fluorinated nucleosides and their analogues represent a class of organic fluorine-containing compounds that, over the last three decades, have found extensive applications in biological chemistry, life-science, and medicine. To date there are a large number of marketed drugs, so called fluorinated purine and pyrimidine antimetabolites, that are broadly used for the treatment of numerous cancers and viral infections (Figure 1).[1c,1d]

Inspired by the relevance of fluorinated purine and pyrimidine nucleosides and taking into account our experience[3] in the design and synthesis of fluorinated purines, their nucleosides and isosteres as potential drug-like scaffolds, our laboratory has undertaken this study to develop a new class of pyrimidine C-ribosides with polyfluoroalkyl substituents in the 4-position by the annulation of the pyrimidine core onto 1-(β-D-ribofuranosyl)formamidine **3**. At the same time, the inclusion of this prospective building-block in the design of diverse C-riboside libraries by the reaction of **3** with the a set of common nonfluorinated 1,3-CCC-bielectrophiles was our second target.

The most fruitful approach described for the synthesis of C-nucleosides (the linkage originates from the C-1′ position of the ribose sugar moiety and joins the carbon of the heterocyclic base) involves the preparation of the desired heterocycle from a C-glycosyl derivative functionalized at the C-1′ substituent. One type of C-glycosyl derivative that has received much attention is represented by the 3-(ribofuranosyl)propiolates **1**, some of which have been utilized to prepare triazole and pyrazole C-nucleosides through 1,3-dipolar cycloaddition reactions to the triple bond.[4] Their reactions with guanidine readily affords 6-(β-D-ribofuranosyl)pyrimidines,[5] whereas 2-(D-ribofuranosyl)-2-formylacetates **2** give 5-(β-D-ribofuranosyl)isocytosine.[6]

Another useful C-ribosyl derivative is 1-(β-D-ribofuranosyl)formamidine hydrochloride **3** (2,5-anhydro-D-allonamidine hydrochloride, Figure 2), which reacted with appropriate dielectrophilic substrates, such as dimethyl cyanoiminodithiocarbonate, ethyl acetoacetate, sodium diethyl oxaloacetate, and ethyl 4-(dimethylamino)-2-oxo-3-buteno-

[a] Institut für Chemie, Universität Rostock,
Albert-Einstein-Str. 3a, 18059 Rostock, Germany
Fax: +49-381-49864112
E-mail: viktor.iaroshenko@uni-rostock.de
iva108@google-mail.com
peter.langer@uni-rostock.de
Homepage: http://www.langer.chemie.uni-rostock.de
[b] National Taras Shevchenko University,
62 Volodymyrska Str., 01033 Kyiv, Ukraine
[c] Department of Chemistry, Ural Federal University,
51 Lenina Ave., 620000 Ekaterinburg, Russia
[d] Leibniz-Institut für Katalyse an der Universität Rostock e.V.,
Albert-Einstein-Str. 29a, 18059 Rostock, Germany
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300107

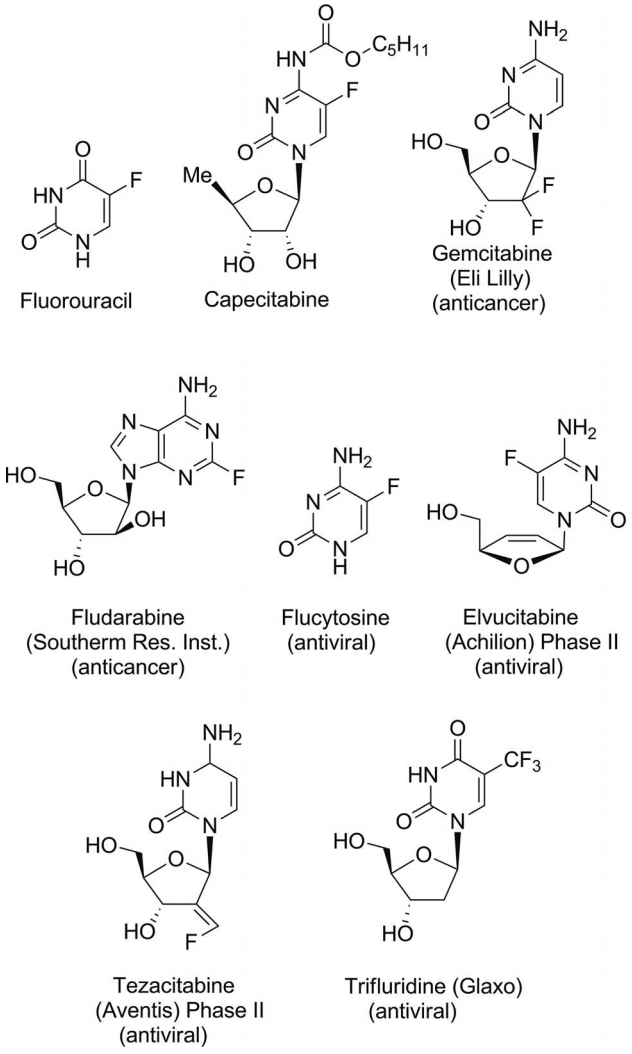



Figure 1. Fluorinated purine and pyrimidine antimetabolites clinically used for the treatment of numerous cancers and viral infections.

ate, to give 2-(β-D-ribofuranosyl)-1,3,5-triazines[7] and 2-(β-D-ribofuranosyl)pyrimidines.[8] However, pyrimidine C-nucleosides with the glycosyl moiety at C-2 have not received much attention despite the fact that some of them are useful in treating a wide variety of diseases, including infections, infestations, neoplasms, and autoimmune diseases.[9]

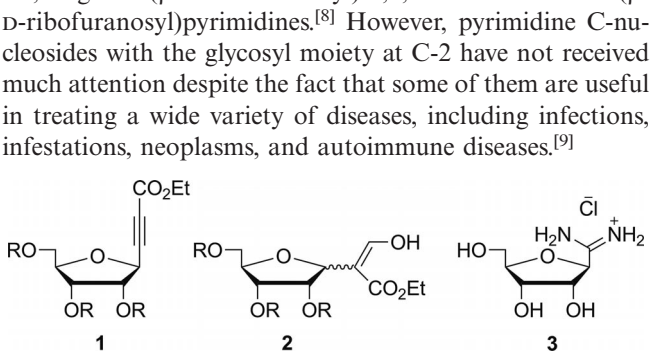
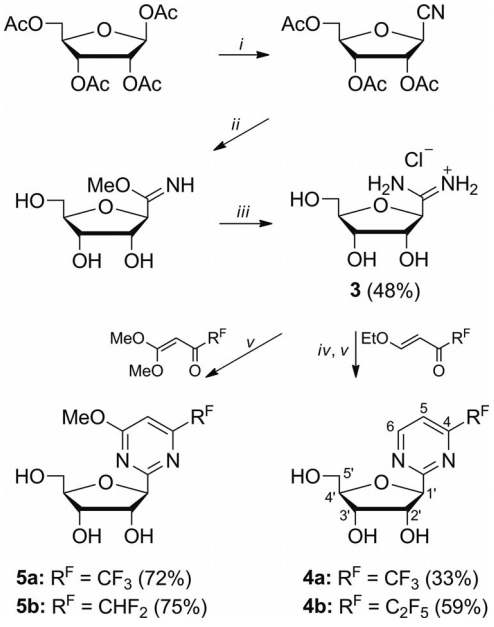



Figure 2. Types of C-1′ glycosyl derivatives.

## Results and Discussion

It is well-known that the inclusion of a $CF_3$ group can have profound and often unexpected results on biological activity and reactivity of the derived fluorinated compounds.[1c,1d] In this context, of special interest is the synthesis of the hitherto unknown $R^F$-containing 2-(β-D-ribofuranosyl)pyrimidines, which may be viewed as partially fluorinated analogues of C-nucleosides that exhibit important biological activities.[9] When the presence of a perfluorinated residue is required in a bioactive target molecule, either the fluoroalkylation reaction[10] of a convenient intermediate or the synthesis from perfluoroalkyl-substituted precursors may be employed.[11,12] When the latter approach is used, 3-alkoxy-1-(polyfluoroalkyl)propen-1-ones are often employed as the electrophilic species for the synthesis of $R^F$-containing compounds.[13] We now report that a perfluoroalkyl chain can be introduced at C-4 of 2-(β-D-ribofuranosyl)pyrimidines by reaction of 3-ethoxy-1-(perfluoroalkyl)propen-1-ones and 3,3-dimethoxy-1-(polyfluoroalkyl)propen-1-ones with 1-(β-D-ribofuranosyl)formamidine hydrochloride **3** (Scheme 1).




Scheme 1. Synthesis of 2-(β-D-ribofuranosyl)-4-(polyfluoroalkyl)-pyrimidines **4** and **5**. *Reagents and conditions:* (*i*) $SnCl_4$, TMSCN, $CH_2Cl_2$, 24 h (room temp.) then 6 h (reflux);[14] (*ii*) MeONa, MeOH, 72 h;[15] (*iii*) $NH_3$ in MeOH, $NH_4Cl$, 72 h;[8] (*iv*) MeONa, DBU, DMF, 80 °C, 3 h (for **4a**); (*v*) $K_2CO_3$, molecular sieves (4 Å), DMF, 60 °C, 4–5.5 h, under argon (for **4b**, **5a**, and **5b**).

The key synthetic intermediate **3**, which had previously been synthesized, was prepared by the reported procedures[8,14,15] from 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl acetate through the O-acetylated cyanide and reaction with catalytic amounts of MeONa in MeOH to give the deblocked methyl β-D-ribofuranosyl-1-carboximidate, which afforded 1-(β-D-ribofuranosyl)formamidine **3** on treatment with methanolic ammonia. Amidine **3** has advantages over functionalized C-glycosides previously used for the synthesis of pyrimidine C-nucleosides. Protecting groups were not required for the synthesis of amidine **3** nor were protecting groups required for its direct use in ring-closure procedures (Scheme 1).[8]

Previously, 4-ethoxy-1,1,1-trifluorobut-3-en-2-one was condensed with acetamidine and benzamidine to give a mixture of the corresponding tetrahydropyrimidines and pyrimidines.[16] After some optimization, we found that treatment of **3** with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one in *N*,*N*-dimethylformamide (DMF) at 80 °C in the presence of MeONa and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in the formation of 2-(β-D-ribofuranosyl)-4-(trifluoromethyl)pyrimidine (**4a**), which is unsubstituted at C-5 and C-6. Perfluoroethylated analogue **4b** was prepared in 59% isolated yield in DMF in the presence of $K_2CO_3$ and molecular sieves (4 Å) at 60 °C.[17] Reaction of **3** with 3,3-dimethoxy-1-(polyfluoroalkyl)propen-1-ones ($R^F$ = $CF_3$, $CHF_2$) under the latter conditions gave 2-(β-D-ribofuranosyl)-6-methoxy-4-$R^F$-pyrimidines **5a** and **5b** in 72–75% yields (Scheme 1). The preparation of compounds **4** and **5** is the first reported synthesis of a pyrimidine ring C-nucleoside containing a polyfluoroalkyl group.[1c,1d,18] The structure of **4a** was confirmed by X-ray single crystal analysis (Figure 3).[19]

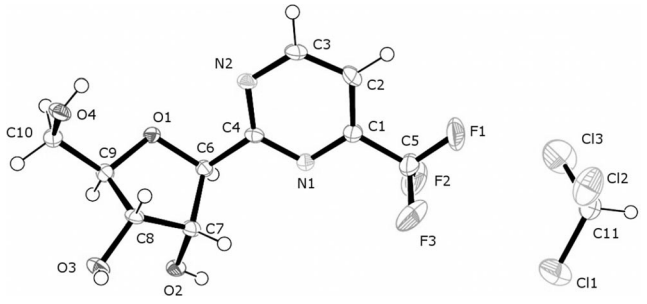
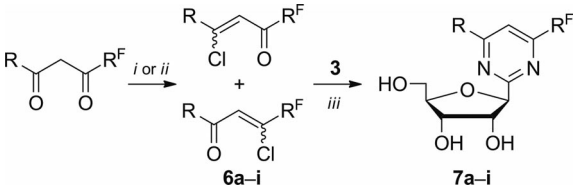



Figure 3. Molecular structure of **4a**.

We decided to include 1-$R^F$-1,3-diketones in this study to obtain the corresponding 6-substituted 2-(β-D-ribofuranosyl)-4-$R^F$-pyrimidines, however, to our great disappointment, this chosen strategy has never been successful in our hands. To overcome this problem, we considered other chemical equivalents of a 1,3-CCC-$R^F$ synthon, namely, a series of α,β-unsaturated chloro ketones **6**, which were obtained starting from easily accessible 1-$R^F$-1,3-diketones by usual chlorination procedures with thionyl chloride ($CHCl_3$, reflux, 3 h, Method A)[20] or oxalyl chloride (DMF, $CH_2Cl_2$, –78 °C to room temp., Method B).[21] The products were distilled under high vacuum to afford a yellow or green liquid consisting of a mixture of *Z*- and *E*-regioisomers **6**, which were not separated (Scheme 2). It was found that treatment of chloro ketones **6** with amidine **3** in DMF in the presence of $K_2CO_3$ and molecular sieves at 0 °C resulted in the formation of 2-(β-D-ribofuranosyl)pyrimidine **7a**–**i** in good yields (38–73%). In most cases, the reaction was complete after 2 h and the products could be isolated by column chromatography. The results are summarized in Table 1 (application of Method A was possible only in the case of perfluoro-substituted diketones and only if they are not sensitive to acids). As can be seen from Table 1, the reaction has virtually no limitations with respect to the nature of the substituents in the chloro ketone molecule. This is therefore a novel and general synthesis of 6-R-4-$R^F$-2-(β-D-ribofuranosyl)pyrimidines **7** with potential biological activity.



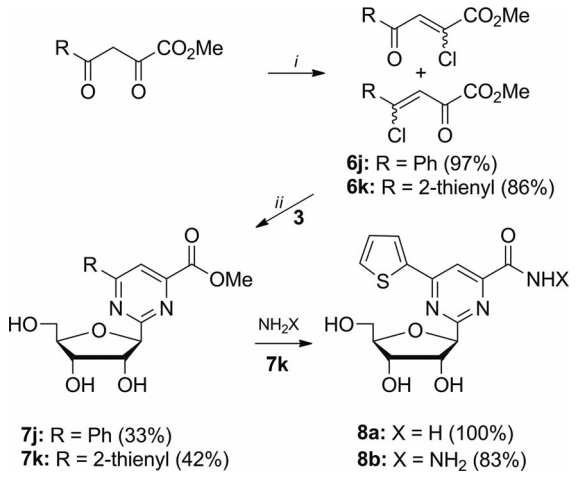

Scheme 2. Synthesis of 2-(β-D-ribofuranosyl)-4-(polyfluoroalkyl)-pyrimidines **7a**–**i** from 1-$R^F$-1,3-diketones. *Reagents and conditions:* (*i*) $SOCl_2$, $CHCl_3$, reflux, 3 h (Method A);[20] (*ii*) oxalyl chloride, DMF, $CH_2Cl_2$, –78 °C to room temp. (Method B);[21] (*iii*) $K_2CO_3$, molecular sieves (4 Å), DMF, 0 °C, 2 h.

Table 1. Yield of compounds **6a**–**i** and **7a**–**i**.

| **6**, **7** | $R^F$ | R | Yield of **6** [%][a][b] | Yield of **7** [%][a] |
|---|---|---|---|---|
| **a** | $CF_3$ | Ph | 92 (A) | 71 |
| **b** | $CF_3$ | 2-thienyl | 81 (A) | 73 |
| **c** | $CF_3$ | 4-$EtC_6H_4$ | 99 (A) | 42 |
| **d** | $CF_3$ | 2-naphthyl | 57 (A) | 38 |
| **e** | $CF_3$ | Me | 52 (B) | 57 |
| **f** | $CF_3$ | *i*Pr | 63 (B) | 55 |
| **g** | $CF_3$ | 2-furyl | 88 (B) | 67 |
| **h** | *n*-$C_3F_7$ | Ph | 93 (A) | 55 |
| **i** | *n*-$C_3F_7$ | 4-$FC_6H_4$ | 74 (A) | 49 |

[a] Yield of pure isolated product. [b] Method A (with $SOCl_2$) or B [with $(COCl)_2$] used to prepare **6** are given in parentheses.

To establish the generality of this cyclization, compound **3** was subjected to analogous reactions with chloroketo esters **6j** and **6k**, prepared from methyl benzoylpyruvate, methyl (2-thenoyl)pyruvate, and oxalyl chloride (Method B), and pyrimidines **7j** and **7k** were obtained under the same conditions in 33 and 42% yields, respectively (Scheme 3). These results clearly show that the present reaction could be applicable to various types of chloro ketones




Scheme 3. Synthesis of 4-(methoxycarbonyl)-2-(β-D-ribofuranosyl)-pyrimidines **7j** and **7k** and their derivatives **8a** and **8b**. *Reagents and conditions:* (*i*) oxalyl chloride, DMF, $CH_2Cl_2$, –78 °C to room temp. (Method B); (*ii*) $K_2CO_3$, molecular sieves (4 Å), DMF, 0 °C, 2 h.

**6**, providing a simple and rapid synthetic route to a wide range of 4,6-disubstituted pyrimidine nucleosides **7**. The structures of products **7** were characterized by IR, $^{1}H$, $^{19}F$, and $^{13}C$ NMR spectroscopic data as well as by MS and HRMS analysis. It should be noted that no α-anomers were observed. All our attempts to synthesize the corresponding ribofuranosylpyrimidines from 4,4,4-trifluoro-1-phenylbutane-1,3-dione, 2-(ethoxymethylene)-4,4,4-trifluoro-1-phenylbutane-1,3-dione, and ethyl 4,4,4-trifluoro-3-oxobutanoate failed.

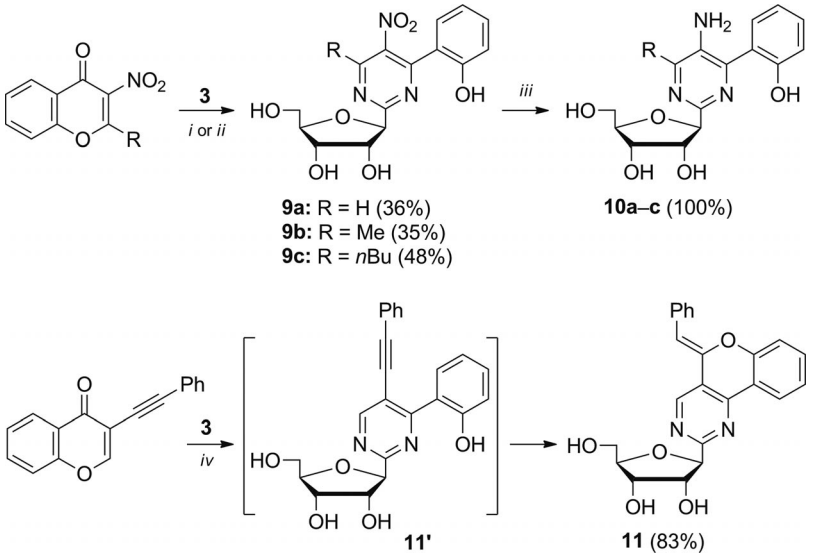
Nucleoside **7k** was employed for the synthesis of other nonfluorinated nucleoside derivatives. When this compound was dissolved in methanolic ammonia and stirred at room temperature overnight, carbamoylpyrimidine **8a**, possessing a ribosyl moiety at the 2-position, was obtained in quantitative yield. Treatment of **7k** with hydrazine hydrate in methanol at room temperature resulted in the formation of hydrazide **8b** in 83% yield (Scheme 3).

It is known that 3-nitro- and 2-methyl-3-nitrochromones[22] react with amidines and guanidine to give the corresponding 5-nitropyrimidines.[23] These reactions proceed by nucleophilic 1,4-addition followed by pyrone ring opening and intramolecular condensation at the carbonyl group. We found that, in the case of amidine **3** and 3-nitrochromone, analogous cyclization took place in the presence of MeONa and $NEt_3$ in MeOH, yielding 5-nitropyrimidine **9a** in 36% yield (Scheme 4). A similar result was obtained with 2-methyl-3-nitro- and 2-butyl-3-nitrochromones in DMF, which gave compounds **9b** and **9c** in 35 and 48% yields, respectively. The reduction of the nitro group of these compounds by hydrogenation in the presence of Pd/C (10 mol-%) afforded the expected 5-aminopyridines **10a**–**c** in quantitative yield.[22]

Li, Duan and Hu[24] condensed 3-iodochromone with phenylacetylene and amidines to give (5*Z*)-5-benzylidene-5*H*-chromeno[4,3-*d*]pyrimidines, the configuration of which was unambiguously established as the *Z* form from X-ray diffraction analysis. Following this precedent for the use of 3-alkynylchromones in pyrimidine synthesis, 3-(phenylethynyl)chromone was treated with C-glycosyl amidine **3** in the presence of $K_2CO_3$ and molecular sieves in DMF to produce benzopyrano[4,3-*d*]pyrimidine **11**, with a glycosyl moiety attached at C-2. This transformation can be rationalized by assuming the initial formation of intermediate **11′** accompanied by intramolecular nucleophilic addition of the hydroxyl group at the triple bond (Scheme 4). We also hoped to increase the scope of this reaction to include 3-(trifluoroacetyl)chromone[25] and 4-chloro-3-(trifluoroacetyl)coumarin,[26] however, these attempts were unsuccessful.

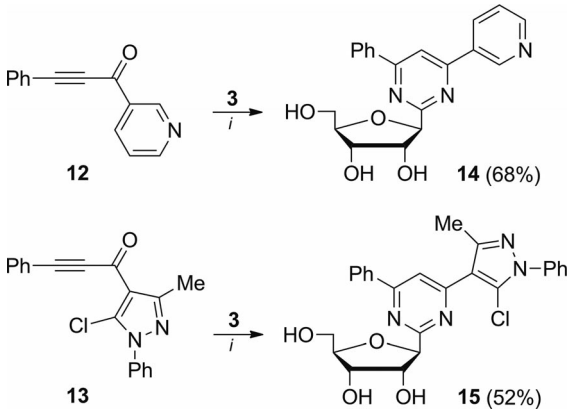
Previously, alkynyl ketones have been condensed with amidines to give pyrimidines.[27] To demonstrate the ability of amidine **3** to add to acetylenic ketones, it was allowed to react with ketones **12** and **13**. It is significant that amidine **3** smoothly reacted with these electrophilic substrates under our reaction conditions ($K_2CO_3$, molecular sieves, DMF) to produce the expected products **14** and **15** in good yields (52–68%; Scheme 5).

In conclusion, we have developed a simple and convenient method for the synthesis of 2-(β-D-ribofuranosyl)pyrimidines, including $R^F$-containing derivatives, by using (β-D-ribofuranosyl)formamidine and various dielectrophilic substrates. These compounds constitute an important structural subunit of a variety of biologically active compounds, and their biological evaluation is being studied in our laboratory. On the other hand, the combinatorial aspect of the synthetic strategies developed here can be used in biology-oriented syntheses of mechanism-based enzyme inhibitors and pitfalls, and UV-active labels for nucleic acids and proteins. Both these aspects are also under intense study in our laboratory.




Scheme 4. Synthesis of C-nucleosides **9**–**11** from 3-nitro- and 3-(phenylethynyl)chromones. *Reagents and conditions:* (*i*) MeONa, $NEt_3$, MeOH, 80 °C, 1.5 h (for **9a**); (*ii*) MeONa, $NEt_3$, DMF, 50 °C, 5 h, under argon (for **9b** and **9c**); (*iii*) $H_2$, Pd (10% on charcoal), MeOH, 2 d; (*iv*) $K_2CO_3$, molecular sieves (4 Å), DMF, 60 °C, 6 h, under argon.




Scheme 5. Synthesis of C-nucleosides **14** and **15** from acetylenic ketones. *Reagents and conditions:* (*i*) $K_2CO_3$, molecular sieves (4 Å), DMF, 70 °C, 4 h, under argon.

## Experimental Section

**General:** All solvents were purified and dried by standard methods. NMR spectra were recorded with Bruker AV 300 and Bruker AV 400 spectrometers. IR spectra were recorded with a Perkin–Elmer FT IR 1600 spectrometer (ATR). Mass spectra were obtained with a Hewlett–Packard GC/MS 5890/5972 instrument (EI, 70 eV) with GC inlet or with an MX-1321 instrument (EI, 70 eV) with direct inlet. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck $60F_{254}$ plates were used for TLC. Chemical yields refer to pure isolated substances.

**2-(β-D-Ribofuranosyl)-4-(trifluoromethyl)pyrimidine (4a):** In a 25 mL flask were placed 1-(β-D-ribofuranosyl)formamidine **3** (0.3 g, 1.41 mmol, 1 equiv.), MeONa (0.069 g, 1.27 mmol, 0.9 equiv.), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.043 g, 0.282 mmol, 0.2 equiv.), and DMF (3 mL), then 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (0.474 g, 2.82 mmol, 2 equiv.) was added and the reaction mixture was stirred at 80 °C for 3 h under argon. After cooling to room temperature, the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography [silica gel (120 g); EtOAc ($R_f$ = 0.08–0.14)], yield 0.130 g (33%); white solid; m.p. 93–95 °C. $^1$H NMR (300 MHz, [$D_6$]DMSO): $\delta$ = 3.50–3.60 (m, 1 H, 5′-Ha), 3.61–3.71 (m, 1 H, 5′-Hb), 3.93–4.01 (m, 1 H, 4′-H), 4.02–4.11 (m, 1 H, 3′-H), 4.22–4.30 (m, 1 H, 2′-H), 4.70 (dd, $J$ = 6.6, 4.7 Hz, 1 H, 5′-OH), 4.92 (d, $J$ = 4.7 Hz, 1 H, 1′-H), 5.04 (d, $J$ = 5.9 Hz, 1 H, 3′-OH), 5.28 (d, $J$ = 5.7 Hz, 1 H, 2′-OH), 8.02 (d, $J$ = 5.1 Hz, 1 H, 5-H), 9.25 (d, $J$ = 5.1 Hz, 1 H, 6-H) ppm. $^{13}$C NMR (63 MHz, [$D_6$]DMSO): $\delta$ = 63.0 ($CH_2OH$), 72.3 (CH-3′), 76.8 (CH-2′), 86.1 (CH-4′), 86.5 (CH-1′), 117.3 (CH-5), 121.5 [q, $^1J_{C,F}$ = 275.2 Hz, $CF_3$], 154.9 (q, $^2J_{C,F}$ = 35.6 Hz, C-4), 162.1 (CH-6), 170.3 (C-2) ppm. $^{19}$F NMR (282 MHz, [$D_6$]DMSO): $\delta$ = –68.6 (s, $CF_3$) ppm. MS (GC, 70 eV): *m*/*z* (%) = 280 (0.36) [M]$^+$], 203 (11) [M – $CF_3$]$^+$, 191 (100), 189 (18), 178 (17), 177 (33). HRMS (ESI): calcd. for $C_{10}H_{12}F_3N_2O_4$ [M + H]$^+$ 281.07437; found 281.07441. IR (ATR): $\tilde{\nu}$ = 3390 (m), 3153 (m), 2979 (w), 2929 (w), 2817 (w), 1588 (w), 1576 (m), 1462 (w), 1449 (w), 1418 (m), 1337 (s), 1320 (w), 1307 (m), 1295 (w), 1250 (w), 1225 (w), 1202 (m), 1171 (s), 1150 (s), 1119 (s), 1100 (m), 1079 (s), 1042 (m), 1002 (w), 975 (w), 909 (m), 887 (m), 851 (m), 800 (w), 761 (m), 719 (m), 703 (m), 677 (s), 649 (s), 586 (w), 542 (m), 528 (m) cm$^{-1}$.

**4-Methoxy-2-(β-D-ribofuranosyl)-6-(trifluoromethyl)pyrimidine (5a):** In a 25 mL flask were placed 1-(β-D-ribofuranosyl)formamidine **3** (0.2 g, 0.94 mmol, 1 equiv.), 1,1,1-trifluoro-4,4-dimethoxy-3-buten-2-one (0.190 g, 1.03 mmol, 1.1 equiv.), $K_2CO_3$ (0.26 g, 1.88 mmol, 2 equiv.), molecular sieves (0.3 g, 4 Å), and DMF (4 mL), and the reaction mixture was stirred at 60 °C for 5.5 h under argon. After cooling to room temperature, the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude residue was purified by short-path column chromatography [silica gel (10 g); $CHCl_3$ (400 mL), then EtOAc ($R_f$ = 0.19–0.29)]. The EtOAc fraction was evaporated to give the desired product, yield 0.209 g (72%); white solid; m.p. 129 °C. $^1$H NMR (300 MHz, [$D_6$]DMSO): $\delta$ = 3.52–3.63 (m, 1 H, 5′-Ha), 3.63–3.72 (m, 1 H, 5′-Hb), 3.92–4.00 (m, 1 H, 4′-H), 4.06 (s, 3 H, MeO), 4.06–4.14 (m, 1 H, 3′-H), 4.20–4.27 (m, 1 H, 2′-H), 4.65 (dd, $J$ = 6.8, 4.7 Hz, 1 H, 5′-OH), 4.80 (d, $J$ = 4.0 Hz, 1 H, 1′-H), 5.00 (d, $J$ = 6.0 Hz, 1 H, 3′-OH), 5.28 (d, $J$ = 5.7 Hz, 1 H, 2′-OH), 7.45 (s, 1 H, 5-H) ppm. $^{13}$C NMR (63 MHz, [$D_6$]DMSO): $\delta$ = 55.7 (MeO), 63.0 ($CH_2OH$), 72.4 (C-3′), 76.6 (CH-2′), 85.7 (CH-4′), 86.6 (CH-1′), 105.3 (CH-5), 121.5 (q, $^1J_{C,F}$ = 274.6 Hz, $CF_3$), 155.3 (q, $J_{C,F}$ = 35.0 Hz), 171.0, 171.7 ppm. $^{19}$F NMR (282 MHz, [$D_6$]DMSO): $\delta$ = –68.7 (s, $CF_3$) ppm. MS (EI, 70 eV): *m*/*z* (%) = 311 (1.74) [M + H]$^+$, 310 (1.25) [M]$^+$, 233 (12), 222 (16), 221 (100), 219 (27), 208 (16), 207 (90), 205 (19), 68 (11). HRMS (ESI): calcd. for $C_{11}H_{14}F_3N_2O_5$ [M + H]$^+$ 311.08493; found 311.08440. IR (ATR): $\tilde{\nu}$ = 3346 (m), 3159 (m), 3118 (w), 2966 (w), 2937 (w), 2908 (w), 2889 (w), 1606 (m), 1585 (w), 1558 (m), 1504 (w), 1479 (s), 1456 (w), 1435 (m), 1383 (s), 1348 (m), 1331 (m), 1304 (m), 1267 (m), 1225 (m), 1201 (s), 1186 (m), 1176 (m), 1151 (s), 1140 (s), 1099 (s), 1057 (s), 1034 (s), 1026 (s), 986 (s), 957 (s), 899 (m), 879 (s), 870 (s), 839 (m), 800 (m), 768 (s), 756 (s), 723 (m), 687 (s), 631 (s), 586 (m), 561 (m) cm$^{-1}$.

**4-Phenyl-2-(β-D-ribofuranosyl)-6-(trifluoromethyl)pyrimidine (7a):** Initial diketone was previously activated by conversion into the corresponding α,β-unsaturated β-chloro ketone. To a solution of 4,4,4-trifluoro-1-phenylbutane-1,3-dione (2.0 g, 9.25 mmol, 1 equiv.) in chloroform (6 mL), was added $SOCl_2$ (2.258 g, 27.8 mmol, 3 equiv.), followed by addition of DMF (0.034 g, 0.46 mmol, 0.05 equiv.). The mixture was heated to reflux for 3 h, then the solvent (containing an excess of $SOCl_2$) was evaporated, and the residue was distilled under high vacuum to afford a green liquid consisting of a mixture of isomers **6a** (1.994 g, 92%).

In a 25 mL flask were placed 1-(β-D-ribofuranosyl)formamidine **3** (0.15 g, 0.71 mmol, 1 equiv.), $K_2CO_3$ (0.39 g, 2.82 mmol, 4 equiv.), and DMF (3 mL), then the previously prepared α,β-unsaturated β-chloro ketone **6a** (0.182 g, 0.78 mmol, 1.1 equiv.) was added at 0 °C and the reaction was stirred at this temperature in the presence of molecular sieves (4 Å) for 1.5 h. The mixture was allowed to stand at room temperature overnight (18 h), then the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography [silica gel (40 g), EtOAc ($R_f$ = 0.30–0.39)], yield 0.178 g (71%); light-green solid; m.p. 77–78 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 4.73 (dd, $^2J$ = 12.3, $^3J$ = 1.3 Hz, 1 H, 5′-Ha), 3.93 (br. s, 3 H, OH), 4.04 (dd, $^2J$ = 12.3, $^3J$ = 2.5 Hz, 1 H, 5′-Hb), 4.28 (s, 1 H, 4′-H), 4.41–4.50 (m, 2 H, 2′-H, 3′-H), 5.27 (d, $^3J$ = 2.7 Hz, 1 H, 1′-H), 7.45–7.60 (m, 3 H, Ph), 7.84 (s 1 H, 5-H), 7.99–8.08 (m 2 H, Ph) ppm. $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ = 62.2 ($CH_2OH$), 71.6 (CH-3′), 78.0 (CH-2′), 85.2 (CH-4′), 85.9 (CH-1′), 111.9 (CH-5), 120.7 (q, $^1J_{C,F}$ = 275.6 Hz, $CF_3$), 127.9 ($CH_{Ar}$), 129.6 ($CH_{Ar}$), 132.7 ($CH_{Ar}$), 135.2, 156.5 (q, $^2J_{C,F}$ = 36.0 Hz, C-6), 167.8, 170.6 ppm. $^{19}$F NMR (282 MHz, $CDCl_3$): $\delta$ = –69.8 (s, $CF_3$) ppm. MS (GC, 70 eV): *m*/*z* (%) = 356 (1.8) [M]$^+$, 268 (15), 267 (100), 253 (32). HRMS (ESI): calcd. for $C_{16}H_{16}F_3N_2O_4$ [M + H]$^+$ 357.10567; found 357.10634. IR (ATR): $\tilde{\nu}$ = 3354 (s), 3078 (w), 2925 (m), 2854 (w), 1595 (s), 1548 (s), 1501 (w), 1479 (w), 1454 (w), 1427 (w), 1388

(s), 1333 (w), 1282 (w), 1261 (s), 1207 (m), 1179 (s), 1136 (s), 1100 (s), 1078 (s), 1051 (s), 1025 (s), 1001 (m), 990 (m), 943 (m), 929 (m), 880 (m), 833 (m), 802 (w), 770 (s), 750 (m), 711 (m), 687 (s), 666 (m), 633 (s), 596 (m), 573 (m), 548 (s) $cm^{-1}$.

**2-(β-D-Ribofuranosyl)-6-(2-thienyl)pyrimidine-4-carboxamide (8a):** Methyl 2-(β-D-ribofuranosyl)-6-(2-thienyl)pyrimidine-4-carboxylate (**7k**; 0.1 g, 0.28 mmol, 1 equiv.) was dissolved in 7 M ammonia solution in methanol (0.81 mL, 5.7 mmol, 20 equiv.) and stirred at room temperature overnight (18 h), then the solvent was evaporated under reduced pressure and the residue was thoroughly dried under high vacuum to give the pure product, yield 0.096 g (100%); white amorphous solid form. $^1$H NMR (300 MHz, [D$_6$]DMSO): $\delta$ = 3.57–3.67 (m, 1 H, 5′-Ha), 3.67–3.77 (m, 1 H, 5′-Hb), 3.94–4.01 (m, 1 H, 4′-H), 4.15–4.23 (m, 1 H, 3′-H), 4.32–4.39 (m, 1 H, 2′-H), 4.74 (dd, $J$ = 6.2, 5.3 Hz, 1 H, 5′-OH), 4.90 (d, $J$ = 4.5 Hz, 1 H, 1′-H), 4.98 (d, $J$ = 5.9 Hz, 1 H, 3′-OH), 5.24 (d, $J$ = 5.5 Hz, 1 H, 2′-OH), 7.31 (dd, $J$ = 4.9, 3.8 Hz, 1 H, 4′′-H), 7.94 (dd, $J$ = 4.9, 1.1 Hz, 1 H, 3′′-H), 8.06 (br. s, 1 H, NH-a), 8.26 (br. s, 1 H, NH-b), 8.28 (dd, $J$ = 3.8, 1.1 Hz, 1 H, 5′′-H), 8.33 (s, 1 H, 5-H) ppm. $^{13}$C NMR (76 MHz, [D$_6$]DMSO): $\delta$ = 63.3 ($CH_2$OH), 72.7 (CH-3′), 76.4 (CH-2′), 85.9 (CH-4′), 86.7 (CH-1′), 111.7 (CH-5), 130.2 ($CH_{Ar}$), 131.0 ($CH_{Ar}$), 133.1 ($CH_{Ar}$), 142.2, 159.1, 161.6, 165.7, 169.2 ppm. MS (EI, 70 eV): $m/z$ (%) = 337 (1) $[M]^+$, 301 (16), 292 (10), 249 (12), 248 (100), 234 (27), 161 (11), 134 (52), 108 (11). HRMS (ESI): calcd. for $C_{14}H_{16}N_3O_5S$ $[M + H]^+$ 338.08052; found 338.08071. IR (ATR): $\tilde{\nu}$ = 3306 (s), 3093 (m), 2928 (m), 2874 (m), 1682 (s), 1574 (s), 1525 (s), 1429 (s), 1394 (s), 1344 (s), 1317 (s), 1228 (m), 1200 (m), 1095 (s), 1078 (s), 1034 (s), 991 (s), 947 (m), 889 (s), 858 (s), 812 (m), 779 (m), 714 (s), 665 (s), 617 (s), 534 (s) $cm^{-1}$.

**4-(2-Hydroxyphenyl)-5-nitro-2-(β-D-ribofuranosyl)pyrimidine (9a):** A sealed ACE pressure tube was charged with 1-(β-D-ribofuranosyl)formamidine **3** (0.3 g, 1.41 mmol, 1 equiv.), MeONa (0.080 g, 1.48 mmol, 1.05 equiv.), AcOH (0.008 g, 0.14 mmol, 0.1 equiv.), $NEt_3$ (0.143 g, 1.41 mmol, 1 equiv.) and MeOH (4.5 mL). After 3-nitrochromone (0.493 g, 1.41 mmol, 1 equiv.) was added, the reaction mixture was stirred at 80 °C for 1.5 h under argon. After cooling to room temperature the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography [silica gel (110 g); EtOAc ($R_f$ = 0.11–0.19)], yield 0.176 g (36%); yellow amorphous solid. $^1$H NMR (300 MHz, [D$_6$]DMSO): $\delta$ = 3.52–3.62 (m, 1 H, 5′-Ha), 3.62–3.72 (m, 1 H, 5′-Hb), 3.95–4.04 (m, 1 H, 4′-H), 4.07–4.16 (m, 1 H, 3′-H), 4.28–4.37 (m, 1 H, 2′-H), 4.71 (dd, $J$ = 6.4, 4.9 Hz, 1 H, 5′-OH), 4.97 (d, $J$ = 4.7 Hz, 1 H, 1′-H), 5.05 (d, $J$ = 5.9 Hz, 1 H, 3′-OH), 5.34 (d, $J$ = 5.7 Hz, 1 H, 2′-OH), 6.94 (dd, $J_1$ = 8.1, 1.0 Hz, 1 H, 3′′-H), 7.07 (td, $J$ = 7.7, 1.0 Hz, 1 H, 5′′-H), 7.45 (ddd, $J$ = 8.1, 7.4, 1.7 Hz, 1 H, 4′′-H), 7.71 (dd, $J$ = 7.7, 1.7 Hz, 1 H, 6′′-H), 9.37 (s, 1 H, 6-H), 10.52 (s, 1 H, 2′′-OH) ppm. $^{13}$C NMR (63 MHz, [D$_6$]DMSO): $\delta$ = 63.0 ($CH_2$OH), 72.5 (CH-3′), 76.9 (CH-2′), 86.1 (CH-4′), 86.5 (CH-1′), 116.4 ($CH_{Ar}$), 120.7 ($CH_{Ar}$), 122.7, 131.5 ($CH_{Ar}$), 133.8 ($CH_{Ar}$), 144.4, 154.2 ($CH_{Ar}$), 156.4, 158.2, 171.7 ppm. MS (EI, 70 eV): $m/z$ (%) = 349 (59) $[M]^+$, 313 (16), 303 (39), 267 (10), 260 (100), 258 (12), 249 (14), 246 (66), 230 (13), 217 (11), 216 (10), 214 (17), 213 (46), 201 (13), 200 (30), 199 (25), 197 (13), 186 (26), 185 (14), 173 (12), 172 (19), 171 (42), 170 (31), 169 (20), 144 (13), 116 (11), 115 (13), 102 (11), 91 (12), 89 (24), 63 (11), 43 (15). HRMS (EI): calcd. for $C_{15}H_{15}N_3O_7$ $[M]^+$ 349.09045; found 349.09066. IR (ATR): $\tilde{\nu}$ = 3242 (s), 2932 (w), 2879 (w), 1606 (w), 1581 (s), 1545 (s), 1524 (m), 1504 (w), 1453 (m), 1427 (m), 1355 (s), 1303 (m), 1265 (m), 1210 (w), 1159 (w), 1070 (s), 1080 (s), 1047 (s), 984 (w), 943 (w), 910 (w), 888 (w), 850 (s), 807 (w), 756 (s), 706 (m), 687 (m), 665 (m), 624 (s), 579 (m), 542 (s) $cm^{-1}$.

**5-Amino-4-(2-hydroxyphenyl)-2-(β-D-ribofuranosyl)pyrimidine (10a):** In a 25 mL flask were placed 4-(2-hydroxyphenyl)-5-nitro-2-(β-D-ribofuranosyl)pyrimidine (**9a**; 0.118 g, 0.34 mmol), Pd/C (0.012 g, 10 wt.-%) and MeOH (3.5 mL). The system was washed three times with argon and then three times with hydrogen. The reaction mixture was stirred for 2 d at room temperature under atmospheric pressure. When the reduction was complete (reaction monitored by TLC), the mixture was filtered through a Celite pad (2–3 cm), which was washed three times with MeOH. The filtrate was evaporated under reduced pressure and the residue was thoroughly dried under high vacuum to give the pure product, yield 0.108 g (100%); pale-yellow amorphous solid form. $^1$H NMR (300 MHz, [D$_6$]-DMSO): $\delta$ = 3.50 (dd, $J$ = 11.7, 3.8 Hz, 1 H, 5′-Ha), 3.65 (dd, $J$ = 11.7, 3.7 Hz, 1 H, 5′-Hb), 3.88–3.97 (m, 1 H, 4′-H), 4.05–4.13 (m, 1 H, 3′-H), 4.18–4.27 (m, 1 H, 2′-H), 4.76 (d, $J$ = 4.5 Hz, 1 H, 1′-H), 4.78–5.86 (br. m, 5 H, OH, $NH_2$), 6.94–7.06 (m, 2 H, 3′′-H, 5′′-H), 7.31–7.79 (m, 1 H, 4′′-H), 7.45 (dd, $J$ = 7.7, 1.5 Hz, 1 H, 6′′-H), 8.29 (s, 1 H, 6-H), 10.44 (br. s, 1 H, 2′′-OH) ppm. $^{13}$C NMR (63 MHz, [D$_6$]DMSO): $\delta$ = 62.9 ($CH_2$OH), 72.2 (CH-3′), 76.6 (CH-2′), 85.4 (CH-4′), 86.4 (CH-1′), 117.3 ($CH_{Ar}$), 120.3 ($CH_{Ar}$), 124.3, 131.4 ($CH_{Ar}$), 131.6 ($CH_{Ar}$), 140.1, 144.7 ($CH_{Ar}$), 149.2, 156.0, 157.2 ppm. MS (EI, 70 eV): $m/z$ (%) = 319 (54) $[M]^+$, 230 (100), 217 (12), 216 (83), 214 (14), 201 (10). HRMS (EI): calcd. for $C_{15}H_{17}N_3O_5$ $[M]^+$ 319.11627; found 319.11684. IR (ATR): $\tilde{\nu}$ = 3324 (s), 3207 (s), 2928 (m), 2873 (m), 1633 (w), 1608 (w), 1568 (m), 1558 (m), 1549 (w), 1504 (w), 1495 (w), 1488 (w), 1447 (s), 1418 (m), 1398 (m), 1327 (m), 1295 (m), 1249 (m), 1206 (m), 1158 (w), 1097 (s), 1082 (s), 1047 (s), 985 (m), 911 (m), 889 (m), 857 (m), 831 (m), 799 (m), 756 (s), 700 (s), 667 (s), 633 (s), 596 (s), 534 (s) $cm^{-1}$.

**(5*Z*)-5-Benzylidene-2-(β-D-ribofuranosyl)-5*H*-chromeno[4,3-*d*]-pyrimidine (11):** In a 25 mL flask were placed 1-(β-D-ribofuranosyl)formamidine **3** (0.15 g, 0.71 mmol, 1 equiv.), 3-(phenylethynyl)-chromone (0.174 g, 0.71 mmol, 1 equiv.), $K_2CO_3$ (0.293 g, 2.1 mmol, 3 equiv.), molecular sieves (0.225 g, 4 Å), and DMF (3 mL), and the reaction mixture was stirred at 60 °C for 6 h under argon. After cooling to room temperature, the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude product was recrystallized from MeOH to afford the pure product, yield 0.237 g (83%); yellow solid; m.p. 204–206 °C. $^1$H NMR (300 MHz, [D$_6$]DMSO): $\delta$ = 3.56–3.69 (m, 1 H, 5′-Ha), 3.70–3.81 (m, 1 H, 5′-Hb), 3.97–4.06 (m, 1 H, 4′-H), 4.12–4.22 (m, 1 H, 3′-H), 4.28–4.37 (m, 1 H, 2′-H), 4.84–4.95 (m, 2 H, 1′-H, 5′-OH), 5.03 (d, $J$ = 6.1 Hz, 1 H, 3′-OH), 5.29 (d, $J$ = 5.7 Hz, 1 H, 2′-OH), 6.77 (s, 1 H, =CH-Ph), 7.23–7.38 (m, 3 H, Ar), 7.41–7.51 (m, 2 H, Ar), 7.56–7.65 (m, 1 H, Ar), 7.89 (d, $J$ = 7.6 Hz, 1 H, Ar), 8.20–8.27 (m, 1 H, Ar), 9.34 (s, 1 H, 6-H) ppm. $^{13}$C NMR (63 MHz, [D$_6$]DMSO): $\delta$ = 63.1 ($CH_2$OH), 72.4 (CH-3′), 76.8 (CH-2′), 85.7 (CH-4′), 86.9 (CH-1′), 106.5 (CH), 117.5 (CH), 118.9, 120.3, 124.6 ($CH_{Ar}$), 125.2 ($CH_{Ar}$), 127.9 ($CH_{Ar}$), 129.5 ($CH_{Ar}$), 129.8 ($CH_{Ar}$), 135.1 ($CH_{Ar}$), 135.4, 144.2, 152.4, 154.3 ($CH_{Ar}$), 155.5, 169.2 ppm. MS (EI, 70 eV): $m/z$ (%) = 405 (64) $[M + H]^+$, 404 (100) $[M]^+$, 368 (20), 316 (56), 315 (99), 314 (51), 313 (30), 302 (50), 301 (88), 300 (15), 299 (12), 286 (23), 285 (32), 273 (13), 272 (11), 271 (32), 256 (11), 247 (16), 246 (78), 206 (15), 189 (12), 128 (12), 73 (11), 44 (16), 43 (14). HRMS (ESI): calcd. for $C_{23}H_{21}N_2O_5$ $[M + H]^+$ 405.14450; found 405.14481. IR (ATR): $\tilde{\nu}$ = 3273 (s), 3064 (m), 2916 (m), 2871 (w), 1658 (w), 1644 (w), 1607 (m), 1595 (m), 1573 (m), 1543 (m), 1494 (w), 1461 (m), 1447 (m), 1424 (m), 1415 (m), 1392 (w), 1331 (m), 1316 (m), 1281 (m), 1242 (m), 1210 (w), 1189 (w), 1161 (w), 1098 (s), 1052 (s), 1043 (s), 1019 (m), 985 (m), 942 (w), 908 (m), 865 (m), 837 (w), 825 (w), 813 (w), 792 (w),

759 (s), 746 (s), 731 (m), 716 (m), 687 (s), 675 (m), 665 (m), 639 (s), 627 (s), 606 (m), 551 (m) $cm^{-1}$.

**4-Phenyl-6-(pyridin-3-yl)-2-(β-D-ribofuranosyl)pyrimidine (14):** In a 25 mL flask were placed 1-(β-D-ribofuranosyl)formamidine **3** (0.2 g, 0.94 mmol, 1 equiv.), 3-phenyl-1-(pyridin-3-yl)propyn-1-one (0.195 g, 0.94 mmol, 1 equiv.), $K_2CO_3$ (0.26 g, 1.88 mmol, 2 equiv.), molecular sieves (0.3 g, 4 Å), and DMF (4 mL), and the reaction mixture was stirred at 70 °C for 4 h under argon. After cooling to room temperature, the inorganic precipitate was filtered off and the filtrate was evaporated under reduced pressure. The crude residue was purified by short-path column chromatography [silica gel (12 g), $CHCl_3$ (1 L), then EtOAc (1.5 L; $R_f$ = 0.03–0.09)]. The EtOAc fraction was evaporated to give the desired product, yield 0.156 g (68%); yellow amorphous solid. $^1H$ NMR (300 MHz, [D$_6$]DMSO): $\delta$ = 3.60–3.71 (m, 1 H, 5′-Ha), 3.72–3.81 (m, 1 H, 5′-Hb), 4.01–4.08 (m, 1 H, 4′-H), 4.21–4.29 (m, 1 H, 3′-H), 4.39–4.47 (m, 1 H, 2′-H), 4.86 (dd, $J$ = 6.2, 4.9 Hz, 1 H, 5′-OH), 5.02 (d, $J$ = 4.2 Hz, 1 H, 1′-H), 5.03 (d, $J$ = 5.9 Hz, 1 H, 3′-OH), 5.28 (d, $J$ = 5.5 Hz, 1 H, 2′-OH), 7.60–7.71 (m, 4 H, Ph), 8.37–8.45 (m, 2 H, Ar), 8.65 (s, 1 H, 5-H), 8.69–8.75 (m, 1 H, Ar), 8.78–8.85 (m, 1 H, Ar), 9.55 (s, 1 H, Ar) ppm. $^{13}C$ NMR (63 MHz, [D$_6$]DMSO): $\delta$ = 63.2 ($CH_2OH$), 72.7 (CH-3′), 76.8 (CH-2′), 85.7 (CH-4′), 87.4 (CH-1′), 112.8 (CH-5), 124.9 ($CH_{Ar}$), 128.4 ($CH_{Ar}$), 129.9 ($CH_{Ar}$), 132.3 ($CH_{Ar}$), 132.9, 135.8 ($CH_{Ar}$), 137.1, 149.6 ($CH_{Ar}$), 152.7 ($CH_{Ar}$), 163.3, 165.4, 169.9 ppm. MS (EI, 70 eV): $m/z$ (%) = 365 (9.1) $[M]^+$, 277 (29), 276 (100), 274 (14), 263 (20), 262 (75), 248 (10), 247 (16), 234 (14), 233 (13), 105 (12), 104 (12). HRMS (ESI): calcd. for $C_{20}H_{20}N_3O_4$ $[M + H]^+$ 366.14483; found 366.14506. IR (ATR): $\tilde{\nu}$ = 3271 (m), 3063 (m), 2918 (m), 2872 (m), 1585 (s), 1574 (s), 1556 (m), 1531 (s), 1504 (m), 1485 (m), 1471 (m), 1452 (m), 1427 (m), 1417 (m), 1410 (m), 1365 (s), 1331 (m), 1294 (m), 1244 (m), 1192 (m), 1101 (s), 1078 (s), 1043 (s), 1026 (s), 1001 (s), 991 (s), 941 (m), 876 (m), 827 (m), 818 (m), 768 (s), 743 (s), 690 (s), 665 (s), 633 (s), 540 (s) $cm^{-1}$.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures, characterization data, and $^1H$, $^{19}F$, $^{13}C$ NMR spectra of all compounds.


[1] a) K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013–1029; b) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; c) J.-P. Begue, D. Bonnet-Delpont, *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, **2008**, p. 366 [ISBN-10: 0–47027–830–7]; d) V. Gouverneur, K. Müller, *Fluorine in Pharmaceutical and Medicinal Chemistry*, Imperial College Press **2012** [ISBN-10: 1–84816–634–6].

[2] a) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319; b) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; d) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643; e) P. Shah, A. D. Westwell, *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 527–540; f) P. Liu, A. Sharon, C. K. Chu, *J. Fluorine Chem.* **2008**, *129*, 743–766; g) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

[3] a) V. O. Iaroshenko, D. V. Sevenard, A. V. Kotljarov, D. M. Volochnyuk, A. O. Tolmachev, V. Y. Sosnovskikh, *Synthesis* **2009**, 731–740; b) V. O. Iaroshenko, *Synthesis* **2009**, 3967–3974; c) V. O. Iaroshenko, D. Ostrovskyi, A. Petrosyan, S. Mkrtchyan, A. Villinger, P. Langer, *J. Org. Chem.* **2011**, *76*, 2899–2903; d) V. O. Iaroshenko, Y. Wang, D. V. Sevenard, D. M. Volochnyuk, *Synthesis* **2009**, 1851–1857; e) V. O. Iaroshenko, Y. Wang, B. Zhang, D. Volochnyuk, V. Y. Sosnovskikh, *Synthesis* **2009**, 2393–2402; f) J. Hussner, R. Begunk, V. O. Iaroshenko, S. Mkrtchyan, M. Hein, L. Supe, K. Sternberg, P. Langer, S. Bien, K.-P. Schmitz, H. K. Kroemer, H. Meyer zu Schwabedissen, Deutsche Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie e. V., Abstracts of the 77th Annual Meeting, **2011**, Frankfurt/M., Germany, vol. 383, p. 19, Supplement 1, *Pyrazolinone derivatives selectively influence the proliferation of HCASMC – A new approach of preventing in-stent restenosis*; g) V. O. Iaroshenko, M. Vilches-Herrera, A. Gevorgyan, K. Arakelyan, D. Ostrovskyi, M. S. A. Abbasi, S. Mkrtchyan, L. Supe, A. Hakobyan, A. Villinger, D. M. Volochnyuk, A. Tolmachev, *Tetrahedron* **2013**, *69*, 1217–1228.

[4] F. G. De Las Heras, S. Y.-K. Tam, R. S. Klein, J. J. Fox, *J. Org. Chem.* **1976**, *41*, 84–90.

[5] S. Y.-K. Tam, R. S. Klein, F. G. de las Heras, J. J. Fox, *J. Org. Chem.* **1979**, *44*, 4854–4862.

[6] C. K. Chu, K. A. Watanabe, J. J. Fox, *J. Heterocycl. Chem.* **1975**, *12*, 817–818.

[7] T. A. Riley, W. J. Hennen, N. K. Dalley, B. E. Wilson, R. K. Robins, *J. Heterocycl. Chem.* **1986**, *23*, 1709–1714.

[8] T. A. Riley, W. J. Hennen, N. K. Dalley, B. E. Wilson, R. K. Robins, S. B. Larson, *J. Heterocycl. Chem.* **1987**, *24*, 955–964.

[9] K. Ramasamy, R. Tam, D. Averett, EP 1254911, 2002.

[10] O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521.

[11] T. Hiyama, *Organofluorine Compounds: Chemistry and Application*, Springer, Berlin, **2000**.

[12] a) J. T. Welch, *Tetrahedron* **1987**, *43*, 3123–3197; b) P. Lin, J. Jiang, *Tetrahedron* **2000**, *56*, 3635–3671; c) G. Resnati, *Tetrahedron* **1993**, *49*, 9385–9445.

[13] a) S. V. Druzhinin, E. S. Balenkova, V. G. Nenajdenko, *Tetrahedron* **2007**, *63*, 7753–7808; b) V. G. Nenajdenko, E. S. Balenkova, *ARKIVOC (Gainesville, FL, U.S.)* **2011**, (*i*), 246–328.

[14] a) M. T. Reetz, I. Chatziiosifidis, H. Kuenzer, H. Mueller-Starke, *Tetrahedron* **1983**, *39*, 961–966; b) K. Utimoto, Y. Wakabayashi, T. Horiie, M. Inoue, Y. Shishiyama, M. Obayashi, H. Nozaki, *Tetrahedron* **1983**, *39*, 967–974.

[15] a) M. S. Poonian, E. F. Nowoswiat, *J. Org. Chem.* **1980**, *45*, 203–208; b) M. S. Poonian, E. F. Nowoswiat, *J. Org. Chem.* **1977**, *42*, 1109–1110.

[16] N. Zanatta, M. B. Fagundes, R. Ellensohn, M. Marques, H. G. Bonacorso, M. A. P. Martins, *J. Heterocycl. Chem.* **1998**, *35*, 451–456.

[17] L. Arista, A. Checchia, G. Gentile, D. Hamprecht, F. Micheli, WO 022934, **2007**.

[18] H. Wójtowicz-Rajchel, *J. Fluorine Chem.* **2012**, *143*, 11–48.

[19] Crystallographic data (excluding structure factors) for the structure **4a** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-923959 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.

[20] K. I. Pashkevich, M. B. Bobrov, A. Y. Aizikovich, M. N. Rudaya, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1986**, 2125–2127.

[21] a) G. Alvernhe, A. Bensadat, A. Ghobsi, A. Laurent, E. Laurent, *J. Fluorine Chem.* **1997**, *81*, 169–172; b) R. E. Mewshaw, *Tetrahedron Lett.* **1989**, *30*, 3753–3756; c) S. A. Popov, A. V. Tkachev, *Synth. Commun.* **2001**, *31*, 233–244.

[22] V. O. Iaroshenko, S. Mkrtchyan, A. Gevorgyan, M. Vilches-Herrera, D. V. Sevenard, A. Villinger, T. V. Ghochikyan, A. Saghiyan, V. Y. Sosnovskikh, P. Langer, *Tetrahedron* **2012**, *68*, 2532–2543.

[23] a) G. Haas, J. L. Stanton, T. Winkler, *J. Heterocycl. Chem.* **1981**, *18*, 619–622; b) K. Takagi, M. Tanaka, Y. Murakami, K. Ogura, K. Ishii, H. Morita, T. Aotsuka, *J. Heterocycl. Chem.* **1987**, *24*, 1003–1007; c) M. Tanaka, Y. Murakami, H. Morita, K. Takagi, *Chem. Pharm. Bull.* **1985**, *33*, 2129–2132.

[24] D. Li, S. Duan, Y. Hu, *J. Comb. Chem.* **2010**, *12*, 895–899.

[25] a) V. Y. Sosnovskikh, R. A. Irgashev, *Synlett* **2005**, 1164–1166; b) V. Y. Sosnovskikh, R. A. Irgashev, M. A. Barabanov, *Synthesis* **2006**, 2707–2718; c) A. Kotljarov, V. O. Iaroshenko,

D. M. Volochnyuk, R. A. Irgashev, V. Y. Sosnovskikh, *Synthesis* **2009**, 3869–3879; d) A. Kotljarov, R. A. Irgashev, V. O. Iaroshenko, D. V. Sevenard, V. Y. Sosnovskikh, *Synthesis* **2009**, 3233–3242; e) V. O. Iaroshenko, I. Savych, A. Villinger, V. Y. Sosnovskikh, P. Langer, *Org. Biomol. Chem.* **2012**, *10*, 9344–9348.

[26] V. O. Iaroshenko, F. Erben, S. Mkrtchyan, A. Hakobyan, M. Vilches-Herrera, S. Dudkin, A. Bunescu, A. Villinger, V. Y. Sosnovskikh, P. Langer, *Tetrahedron* **2011**, *67*, 7946–7955.

[27] R. M. Adlington, J. E. Baldwin, D. Catterick, G. J. Pritchard, *Chem. Commun.* **1997**, *18*, 1757–1758.

Received: January 19, 2013
Published Online: April 4, 2013